Histone Acetylation Regulates Intracellular pH.

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Public Summary:
This work revealed a fundamentally novel function for chromatin which is the physiologically relevant form of the human genome. We found that the histone proteins around which the DNA wraps function as a buffer to prevent fluctuations in the level of the acidity of the cell. Histones are normally modified by a small chemical group called acetylation. Different cell types have different levels of acetylation such as embryonic stem cells which have high levels or resting, non-dividing cells which have low levels. The levels of histone acetylation are also related to the aggressiveness of cancer cells. Despite these observations, it has been unclear what function the differences in histone acetylation serve for the cell. Because of the intimate association of histones with DNA, it was previously thought that histone acetylation affects only DNA-based processes. However, in this paper we showed that histone acetylation serves to regulate intracellular acidity of the cell. Cells that are acidic have low levels of histone acetylation to counteract further acidification. When cells are more alkaline, they have high levels of acetylation. Our data have revealed a fundamental biological process which has implications for therapeutic use of a class of drugs that are commonly used in clinic as well as in research.

Scientific Abstract:
Differences in global levels of histone acetylation occur in normal and cancer cells, although the reason why cells regulate these levels has been unclear. Here we demonstrate a role for histone acetylation in regulating intracellular pH (pH(i)). As pH(i) decreases, histones are globally deacetylated by histone deacetylases (HDACs), and the released acetate anions are coexported with protons out of the cell by monocarboxylate transporters (MCTs), preventing further reductions in pH(i). Conversely, global histone acetylation increases as pH(i) rises, such as when resting cells are induced to proliferate. Inhibition of HDACs or MCTs decreases acetate export and lowers pH(i), particularly compromising pH(i) maintenance in acidic environments. Global deacetylation at low pH is reflected at a genomic level by decreased abundance and extensive redistribution of acetylation throughout the genome. Thus, acetylation of chromatin functions as a rheostat to regulate pH(i) with important implications for mechanism of action and therapeutic use of HDAC inhibitors.